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(54) Title: OPHTHALMIC COMPOSITION

(57) Abstract: This invention is directed to ophthalmic compositions comprising an ascomycin for once-a-day administration.

Ophthalmic composition

This invention relates to ophthalmic compositions, e.g. gels, comprising an ascomycin or a compound of the FK 506 class for once-a-day administration.

We have found that ophthalmic compositions have often to be applied typically two to four times a day and that such repeated administration is not optimal in practice, e.g. for optimal treatment the patient has to have the medicament always available and the patient is disturbed several times a day. Such multiple administration of a drug, in particular of an ophthalmic composition, leads generally to the problem of overdosing and/or underdosing. Overdosing may typically generate ocular irritation, whereas underdosing may typically lead to reoccurrence of the symptoms.

There is thus a need for a so-called once-a-day administration of ophthalmic drugs.

FK506 is a known macrolide antibiotic that is produced by Streptomyces tsukubaensis No 9993. It is also a potent immunosuppressant. The structure of FK506 is given in the appendix to the Merck Index, 11th Edition as item A5. Methods of preparing FK506 are described in EP 184162. A large number of derivatives, antagonists, agonists and analogues of FK506, which retain the basic structure and at least one of the biological properties (for example immunological properties) of FK506, are known. These compounds are described in a large number of publications, for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385, WO 93/5059 and the like. Ascomycins and derivatives thereof, including FK506, are referred to hereinafter as "ascomycins".

Preferred ascomycins for use in the present invention include FK506; 33-epi-chloro-33-desoxy-ascomycin as disclosed in Example 66a in EP 427680 (hereinafter referred to as Compound A); {[1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16, 20-trihydroxy-4-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-aza-tricyclo[18.6.1.0(1,22)]heptacos-10-ene-2,8,21,27-tetraone as disclosed in Examples 6d and 71 in EP 569 337; and {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-

dioxa-4-aza-tricyclo[22.3.1.0(4,9)]octacosa-5,18-diene-2,3,10,16-tetraone, also known as 5,6-dehydro-ascomycin as disclosed in Example 8 in EP 626 385. Particularly preferred is Compound A.

We have found that compositions comprising an ascomycin may be formulated for once-a-day administration which provide a therapeutic effect of the ascomycin at the eye over 24 hours and such compositions are surprisingly well tolerated. Moreover said once-a-day compositions produce a highly reliable and more reproducible clinical result in a patient treated therewith.

Therefore, in one aspect the present invention provides an ophthalmic composition being adapted for topical once-a-day administration of an ascomycin (hereinafter compositions of the present invention).

The concentration of an ascomycin is preferably from about 0.005 – 3.0%, more preferably from 0.01 – 1.5by weight based on the total weight of the composition. If desired, the compositions of the present invention may be in the form of a suspension, e.g. containing particles of an ascomycin e.g. with a mean particle diameter of 0.2 to 900 nm.

Applicants have found compositions of the present invention with moderate viscosity, e.g. from 50 to 2000, e.g. about 100 to 1000, mPa s at 20-25°C, which are comfortable to apply. Upon instillation into the eye, the viscosity of the compositions of the present invention may increase or decrease. Preferably the viscosity decreases upon instillation into the eye. The compositions of the present invention still have an excellent retention after instillation into the eye.

The compositions of the present invention may comprise pharmaceutically acceptable excipients, which are suitable for ophthalmic compositions. For example the excipients and/or compositions of the present invention should not significantly affect the lacrimal system nor the ocular tear film.

Information on the properties, specifications and characteristics are described e.g in standard texts such as Fiedler, H.P.; 1996; Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; Editio Cantor Verlag Aulendorf (Germany), and Kibbe, A.H.;

2000; Handbook of Pharmaceutical Excipients, a joint publication of Pharmaceutical Press, London (UK), and American Pharmaceutical Association, Washington (US) as well as manufacturers' brochures, the contents of which are incorporated herein by reference.

The compositions of the present invention may typically comprise (1.) biocompatible polymers (thickeners). Such a polymer may be a thermo-reversible polymer e.g. one which increases the viscosity of the composition on increasing temperature. Additionally such polymers may exhibit muco-adhesive properties.

A wide variety of polymers may be chosen but we have found the following are particularly preferred.

1.1 polyoxyethylene-polyoxypropylene copolymers and preferably block co-polymers. Preferably the polyoxypropylene polymer number is from about 10 to about 60. Preferably the polyoxyethylene polymer number is from about 10 to about 150. Examples include such as those known and commercially available under the trade names Lutrol® and Poloxamer® (Fiedler, loc. cit., p. 1200, 1203; Handbook of Pharmaceutical Excipients, loc. cit., page 386) and in particular Poloxamer® 407 and Lutrol® F127, having a melting point of about 52 to 57°C.

1.2 acrylic acid homo- and co-polymers, which preferably are cross-linked; preferably carboxypolymethylene. Preferred molecular weights are between about 500,000, preferably from 1,000,000 to about 10,000,000 Daltons. Preferably, the acid groups comprise between 56 and 68% by weight of the total polymer.
Preferably it is crosslinked with a polyol, e.g.

1.2.1 with divinyl glycol, such as those known and commercially available under the trade name Noveon® from BFGoodrich, and in particular Noveon® AA-1, or

1.2.2 with allylsucrose or allypentaerythritol, such as those known and comercially available under the trade name Carbopol® from BFGoodrich. Examples include those known and commercially available under the trade name Carbopol® and in particular Carbopol® 934P,974P,980,981 and 984.

The exact amounts of polymer/thickener components may vary within wide limits, e.g. to produce a composition of the present invention within the viscosity indicated above. For example the amount may be from e.g. 0.05 to 10%, by weight of the total composition.

Preferably the present invention provides ophthalmic compositions comprising an ascomycin and at least one polymer such as i) a polyoxyethylene-polyoxypropylene co-polymer or block co-polymer, and ii) a cross-linked acrylic acid polymer, e.g. as hereinabove described, e.g. adapted for topical once-a-day administration to the eye.

Preferably both polymer/thickener components component i) and ii) are present e.g. in a weight ratio of i):ii) of e.g. 1:200 to 1:5, e.g. 1:50 to 1:20.

The compositions of the present invention may further comprise (2.) a tonicity enhancing agent. Suitable tonicity enhancing agents are, e.g.

2.1 ionic compounds, such as alkali metal or alkaline earth metal halides, such as $CaCl_2$, KBr, KCl, LiCl, NaI, NaBr or NaCl, or boric acid, and/or

2.2 non-ionic compounds such as urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose.

Conveniently, sufficient tonicity enhancing agent is added to impart to the ready-for-use ophthalmic composition an osmolality of approximately from 50 to 1000 mOsmol, preferred from 100 to 400 mOsmol, more preferred from 200 to 400 mOsmol and even more preferred from 280 to 350 mOsmol.

For the adjustment of the pH, preferably to a physiological pH, addition of (3.) a pharmaceutically acceptable buffer system. Examples of buffer substances are acetate, ascorbate, borate, hydrogen carbonate/carbonate, citrate, gluconate, lactate, phosphate, propionate and tromethamine (tris-(hydroxymethyl)-aminomethane, TRIS) buffers. Trometh-amine buffer is preferred. The buffer substance added is typically of an amount to ensure and maintain a physiologically tolerable pH range. The pH range is generally in the range of from 4 to 9, preferably from 4.5 to 8.5 and more preferably from 5.0 to 8.2.

The compositions of the present invention may further comprise (4.) a preservative, e.g. on storage or to inhibit microbial growth after opening a closed container holding such a composition and exposing such a composition to the air. A preservative may typically be selected from e.g.

4.1 a quaternary ammonium compound such as e.g. benzalkonium chloride (N-benzyl-N-(C_8-C_{18}-alkyl)-N,N-dimethylammonium chloride), benzoxonium chloride, cetrimide (hexadecyl-trimethylammonium bromide) or the like.

4.2 alkyl-mercury salts of thiosalicylic acid, such as e.g. thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate,

4.3 parabens, such as e.g. methylparaben or propylparaben,

4.4 alcohols, such as e.g. chlorobutanol, benzyl alcohol or phenyl ethanol,

4.5 biguanide derivatives, such as e.g. chlorohexidine or polyhexamethylene biguanide,

4.6 sodium perborate,

4.7 imidazolidinyl urea as known and commercially available under the trade name Germal®II,

4.8 sorbic acid,

4.9 stabilized oxychloro complexes such as known and commercially available under the trade name Purite®,

4.10 polyglycol-polyamine condensation resins, such as known and commercially available e.g. under the trade name Polyquart® from Henkel KGaA, and/or

4.11 a mixture of any components 4.1 to 4.10.

Preferred preservatives are quaternary ammonium compounds, in particular benzalkonium chloride and cetrimide. Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi, e.g. the preferred preservatives are present in an amount of about 0.001-0.02%.

A pharmaceutical composition may additionally require the presence of (5.) a solubilizer, . A solubilizer suitable for an above concerned composition is e.g.

5.1 octylphenoxy-poly(ethylenoxy)-ethanol (tyloxapol) known and commercially available under the trade name Triton®, e.g. Triton ® WR 1339, (Fiedler, loc. cit., p 1609),

5.2 polyethylene glycol glyceryl fatty acid ester. The fatty acid ester may include mono and/or di and/or tri fatty acid ester. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C_8-C_{20}. The polyethylene glycols may have e.g. from 5 to 40 [CH_2-CH_2-O] units, e.g. 5 or 30 units. Particularly suitable is polyethylene glycol (15) glyceryl monostearate or polyethylene glycol (15) glyceryl monooleate which is commercially available, e.g. under the trade

name TGMS®-15 or TGMO®-15, respectively, e.g. from Nikko Chemicals Co., Ltd. Further suitable is polyethylene glycol (30) glyceryl monooleate which is commercially available, e.g. under the trade name Tagat® O, e.g. from Goldschmidt (H. Fiedler, loc cit, vol. 2, p. 1502-1503). Further suitable are polyethylene glycol glyceryl C_8-C_{10} fatty acid ester with from 5 to 10 [CH_2-CH_2-O] units, e.g. 7 units, e.g. Cetiol® HE, or Labrasol®

5.3 polyoxyethylene C_{8-20} fatty acid esters, e.g. polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj® (Fiedler, loc. cit., 2, p. 1042) or Brij® (Fiedler, loc. cit., p. 259; Handbook of Pharmaceutical Excipients, loc. cit., p. 367). An especially preferred product of this class is Myrj® 52 having a D^{25} of about 1.1, a melting point of about 40 to 44°C, an HLB value of about 16.9, an acid value of about 0 to 1 and a saponification value of about 25 to 35,

5.4 glycerol ethers (Fiedler, loc. cit., p.701),

5.5 cyclodextrins, e.g. α-, β- or γ-cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxy-alkylated or alkyloxycarbonyl-alkylated derivatives, or mono- or diglycosyl-α-, β- or γ-cyclodextrin, mono- or dimaltosyl-α-, β- or γ- cyclodextrin or panosyl-cyclodextrin, e.g. such as known and commercially available under the trade name Cavamax® or Cavasol® from Wacker Chemie. An especially preferred product of this class is hydroxypropyl- γ-cyclodextrin, e.g. as known and commercially available under the trade name Cavasol® W7 HP or Cavasol® W8 HP. A mixture of cyclodextrins may also be used.

5.6 polyoxyethylene-sorbitan- C_{8-20} fatty acid esters (polysorbates) e.g. produced by co-polymerising ethylene oxide with fatty acid esters of a sorbitol and its anhydrides of e.g. mono- and tri- lauryl, palmityl, stearyl and oleyl esters e.g. of the type known and commercially available under the trade name Tween® (Fiedler, loc.cit., p.1615) including the products Tween®

20 [polyoxyethylene(20)sorbitanmonolaurate],
21 [polyoxyethylene(4)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
65 [polyoxyethylene(20)sorbitantristearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
81 [polyoxyethylene(5)sorbitanmonooleate],
85 [polyoxyethylene(20)sorbitantrioleate].

Especially preferred products of this class are Tween®20 and Tween®80.

5.7 reaction products of natural or hydrogenated vegetable oils and ethylene glycol, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various tensides available under the trade name Cremophor. Particularly suitable are the products Cremophor RH 40 having a saponification no. ca. 50-60, an acid no.=<1, an iodine no.=<1, a water content (Fischer)=<2%, an n_D^{60} =ca.1,453-1,457 and an HLB=ca. 14-16; Cremophor RH 60 having a saponification no.=ca. 40-50, an acid no. =<1, an iodine no.=<1, a water content (Fischer)=ca. 4.5-5.5%, an n_D^{25}=ca.1.453-1,457 and an HLB=ca.15-17; and Cremophor EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an n_D^{25} =ca.1.471 (c.f. Fiedler loc. cit. p. 326-327). Also suitable for use in this category are the various tensides available under the trade name Nikkol, e.g. Nikkol HCO-60. The said product NIKKOL HC0-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0°C.; Freezing point=ca. 32.4°C.; H_2O content (%, KF)=ca. 0.03, and/or

5.8 mixtures of the components 5.1 to 5.7.

Especially preferred solubilizers are Cremophor EL, Cremophor RH 40, tyloxapol and cyclodextrins. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient, preferably 0.5 to 1000, e.g. 1 to 500.

Further excipients may be comprised in the compositions of the present invention, which may in particular function as a combined stabilizer/solubilizer. Such a combined additional stabilizer/solubilizer is for example a cyclodextrin or a mixture of cyclodextrins. A preferred cyclodextrin is in particular selected from the group of α-cyclodextrin, β-cyclodextrin, γ-cyclo-

dextrin, hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dimethyl-β-cyclodextrin, randomly methylated β-cyclodextrin and dimethyl-γ-cyclodextrin. The amount is generally in the range of from approximately 0.01 to approximately 90% by weight, more preferably in the range of from 0.1 - 20% by weight.

The ophthalmic compositions may comprise further pharmaceutically acceptable excipients, such as (6.) emulsifiers, (7.) wetting agents or (8.) fillers, such as, e.g. the polyethylene glycols (Fiedler, loc. cit., p. 2108, Handbook of Pharmaceutical Excipients, loc. cit., p 392) such as PEG 200, 300, 400 and 600, or Carbowax® 1000, 1500, 4000, 6000 and 10000.

Other excipients that may be used if desired are listed below but they are not intended to limit in any way the scope of the possible excipients. They are especially (9.) complexing agents, such as disodium-ethylenediamine tetraacetate, ethylenediamine tetraacetic acid (EDTA), (10.) antioxidants, such as ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butylated hydroxyanisole, butylated hydroxytoluene or alpha-tocopherol acetate; (11.) stabilizers, such thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol; or (12.) other excipients, such as, for example, lauric acid sorbitol ester, triethanol amine oleate or palmitic acid ester. Preferred exipients are complexing agents, such as disodium-EDTA. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from about 0.0001 to about 90% by weight.

In another embodiment, the present invention provides for compositions further comprising (13.) an ophthalmic carrier. Such carriers are typically adapted for topical administration, and are for example

13.1 water,

13.2 mixtures of water and water-miscible solvents, such as C_1- to C_7-alkanols,

13.3 vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethyl-cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinyl-pyrrolidone,

13.4 water-soluble polymers for ophthalmic uses, such as, for example, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxy-methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropyl-cellulose and hydroxypropylcellulose,

13.5 acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, poly-acrylamides,

13.6 natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, gellan gum such as Gelrite®, xanthan gum, carrageenin, agar and acacia,

13.7 starch derivatives, such as starch acetate and hydroxypropyl starch,

13.8 synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, or

13.9 mixtures of those polymers.

Preferred carriers are water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxy-propylcellulose and hydroxypropylcellulose, or mixtures thereof. The concentration of the carrier is, for example, from 1 to 100 000 times the concentration of the active ingredient.

It will be appreciated that although the excipients have been described above by reference to a particular function any particular excipient may have alternative or multiple functions, e.g. cyclodextrin or a mixture of cyclodextrins may act as e.g. stabilizer, complexing agent and/or solubilizer.

The compositions of the present invention are surprisingly stable, as indicated by conventional tests, e.g. under stressed conditions, such as 15h at 80°C or 1 month at 40°C. The compositions of the present invention are stable over 2, even 3, years showing less than 5 % degradation of the ascomycin at 20 to 30°C. This surprising stability is also observed in an aqueous composition comprising an ascomycin. Such aqueous compositions represent the preferred ophthalmic compositions of the present invention and contain an ascomycin typically in suspension.

A typical example of an aqueous ascomycin suspension contains:

1% Suspension	%	mg/mL
33-epi-chloro-33-desoxy-ascomycin. (Micronised)	1%	10 mg/mL
Pluronic F127 NF (Poloxamer 407)	0.1%	1.0 mg/mL
Carbopol 934P NF	0.2%	2.0 mg/mL
Mannitol, USP	4.3%	43 mg/mL
Benzalkonium Chloride	0.015%	0.15mg/mL
Sodium Hydroxide	* Adjust to pH 6.5	*Adjust to pH 6.5
Water for injection	qs 400g	qs 400g

The present invention is therefore also useful to stabilize an aqueous composition comprising an ascomycin, in particular comprising an ascomycin suspension.

The ophthalmic compositions of the present invention may be prepared in conventional manner e.g. by mixing an ascomycin and appropriate excipients.

Filling may be effected before or after sterilization of the resulting mixture. Sterilization of the composition of the present invention and the primary package can be effected e.g. by gamma irradiation, by ethylene oxide treatment, by electron beam, by autoclaving, by microwave treatment, by filtration through a sterile filter, or by steam sterilization.

The compositions of the present invention may be packaged in conventional manner. The compositions of the present invention may be stored in single or multiple unit dosage form, e.g. closed bottles, tubes or other containers made from glass, plastic such as e.g. poly-ethylene, polyethylene terephthalate, or polypropylene, or metal or combinations thereof. For example bottles may contain about 1 to 10 ml of the compositions of the present invention. The container may be fitted with a dropper to facilitate administration.

The compositions of the present invention may be formulated in conventional manner e.g. to be particularly adapted for topical ophthalmic use. In so far as the procedures for formulation are not particularly described herein such formulation procedures may for example be known in the art, or analogous to those known in the art or to procedures described herein. Representative procedures are disclosed in for example, Remington's Pharmaceutical Sciences, 19th Ed., Mack Publ., Co., 1995, H. Sucker et al, Pharmazeutische Technologie, 2nd Edition, Thieme, 1991, R: H. Mueller et al, Pharmazeutische Technologie: Moderne Arzneimittelformen, 2nd Edition, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1998, L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, and Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. Vol. 7, (Springer Verlag, 1971) as well as later editions, the contents of all of which are incorporated herein by reference.

The excipients used may e.g. be those known in the art e.g in the Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; and Handbook of Pharmaceutical Excipients, references referred to above, or analogous to those known in the art or new excipients having analogous function to those described in the art or herein.

The compositions of the present invention are useful for the treatment of immune-mediated conditions of the eye, such as auto-immune diseases, e.g. dry eye, uveitis, keratoplasty or chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions or corneal transplants, and in particular of dry eye, and may be used for the treatment and prevention of signs and symptoms of the ocular conditions as indicated e.g. in standard animal trials and clinical trials.

One animal test comprises a modified Draize test on three albino rabbits wherein the ocular tolerability after a single dose instillation of 50 microlitres of compositions of the present invention on the ocular surface is shown for the 15 minutes after instillation then after 1, 2 and 7 days. The tolerability was based on visual examination considering the following parameters: discomfort as judged by blinking or partial/complete closure of the eye, duration of discomfort, discharge, redness of conjunctiva (palpebral and bulbar conjunctiva), chemosis of conjunctiva (swelling), degree of opacity of cornea and area of cornea involved, and pathological influence upon iris.

A clinical trial may be effected to test the efficacy and tolerability of about 30 to 40 microlitre of compositions of the present invention containing 1% of an ascomycin administered once a day by instillation onto the ocular surface, e.g. to the inside lower lid, to groups of, e.g. 10 to 25, healthy volunteers, or patients suffering from allergic conjunctivitis. The trial lasts e.g. 8 days.

The subjects are examined to determine the effect against conjunctivitis, e.g. fast onset of action and long duration of action and good tolerability, e.g. lack of significant irritation or reddening.

Additionally the bioavailability of the compositions of the present invention in the above trials may be determined by absorption in the conjunctiva or surrounding tissues.

The bioavailability of an addressed once-a-day ophthalmic composition may be assessed with the pharmacokinetic assay described infra:
A fixed volume, e.g. 50 microliters, of the ophthalmic formulation was instilled onto the upper part of the conjunctiva of rabbits. Tears, bulbar conjunctiva, cornea and sclera were sampled after either 5, 15, 30 minutes, or, 1, 8, 16, or 20 h. Samples were extracted for ascomycin determination related to the wet weight amount of tissue or tears. Ascomycin was determined using a liquid chromatography linked to mass spectrography (LC-MS) validated method.

The retention of an addressed once-a-day ophthalmic composition may be assessed with retention tests described infra:
The upper eyelid of one eye of an albino rabbit is carefully pulled away from the eyeball and 50 microliter of the test substance is instilled on the superior part of the bulbar conjunctiva using a gauged automatic pipette. The eyelid is gently closed for about one second. After either 5 min, 1 hour, 4 hours, 8 hours, 16 hours or 24 hours a weighed Schirmer's test strip is maintained in the cul-de-sac between the inferior lid and the temporal part of the eyeball for exactly one minute. The absorbed tears collected on each Schirmer test strip are immediately weighed and the ascomycin content is determined e.g. after extracting the strips by liquid chromatography/ negative ion chemical ionization mass spectrometry using a deuterated analogue of the ascomycin as internal standard. The strips may be kept frozen up to analytical test of the ascomycin content.

The exact amount of the ascomycin to be administered will naturally depend on a variety of factors, e.g. choice of salt, excipients, formulation properties, and severity of the condition. Conveniently, the composition of the present invention is administered to the cornea once a day, e.g. after breakfast. Preferably from about 25 to about 75 microlitres, e.g. from about 50 to about 75 microlitres, is administered, e.g. using a dropper.

The daily dose of the ascomycin to be administered is from about 1 micrograms/kg to about 5 micrograms/kg. For larger mammals, e.g. a 70 kg mammal such as a human, a dose of from about 100 to about 300 micrograms, is indicated.

Therefore, in a further aspect the present invention provides

a) an ophthalmic composition as defined above for use in the treatment of immune-mediated conditions of the eye, such as auto-immune diseases, e.g. dry eye, uveitis, keratoplasty or chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions or corneal transplants, in particular dry eye, or a condition treatable by ascomycin therapy,

b) a method for treating immune-mediated conditions of the eye, such as auto-immune diseases, e.g. dry eye, uveitis, keratoplasty or chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions or corneal transplants, in particular dry eye, or a condition treatable by ascomycin therapy comprising administering a composition of the present invention to the eye of a patient in need thereof, or

c) the use of a composition of the present invention in the preparation of a medicament for the treatment of immune-mediated conditions of the eye, such as auto-immune diseases, e.g. dry eye, uveitis, keratoplasty or chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions or corneal transplants, in particular dry eye, or a condition treatable by ascomycin therapy.

All percentages referred to herein are weight/weight except where otherwise indicated.

Claims

1. An ophthalmic composition adapted for topical once-a-day administration to the eye comprising an ascomycin.

2. An ophthalmic composition, in particular a composition according to claim 1, comprising an ascomycin and at least one polymer selected from
   i) a polyoxyethylene-polyoxypropylene co-polymer or block co-polymer, and
   ii) an acrylic acid homo- or co-polymer.

3. A composition according to claim 1, wherein said acrylic homo- or co-polymer is crosslinked.

4. A composition according to claim 2 further comprising a tonicity enhancing agent, a buffer, and a preservative.

5. A composition according to claim 2 or 3 further comprising an ophthalmic carrier.

6. A composition according to any preceding claim wherein the ascomycin is 33-epi-chloro-33-desoxy-ascomycin.

7. Method for treating immune-mediated conditions of the eye, such as auto-immune diseases, e.g. dry eye, uveitis, keratoplasty or chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions or corneal transplants comprising administering a composition comprising an ascomycin to the eye of a patient in need thereof.

8. Method for treating dry eye comprising administering an affective amount of a composition of any one of claims 1 to 5 to the eye of a patient in need thereof.

9. Use of a composition according to anyone of claims 1 to 6 in the preparation of a medicament for the treatment of immune-mediated conditions of the eye, such as auto-immune diseases, e.g. dry eye, uveitis, keratoplasty or chronic keratitis; allergic

conditions, e.g. vernal conjunctivitis; inflammatory conditions or corneal transplants or another condition treatable by ascomycin therapy.

10. Use according to claim 9 in the preparation of a medicament for the treatment of dry eye.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: OPHTHALMIC COMPOSITION COMPRISING AN ASCOMYCIN

(57) Abstract: This invention is directed to ophthalmic compositions comprising an ascomycin for once-a-day administration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09408

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K47/32 A61K47/34 A61K9/00 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 34830 A (MA & TCARON ;GALENA A S (CZ); STUCHLIK JOSEF (CZ); STUCHLIK MILAN) 15 July 1999 (1999-07-15)	1,7-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2003	24/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ESTANOL, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09408

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	LIN H-R ET AL: "Carbopol/pluronic phase change solutions for ophthalmic drug delivery" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 69, no. 3, 3 December 2000 (2000-12-03), pages 379-388, XP004221288 ISSN: 0168-3659 page 386 -page 387 ---	1-6
Y	EP 0 551 626 A (LEK TOVARNA FARMACEVTSKIH) 21 July 1993 (1993-07-21) page 5 -page 8; claim 1 ---	1-10
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 7-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/09408

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/09408

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